BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2007.03034.x

# Adverse drug reactions in adult medical inpatients in a South African hospital serving a community with a high HIV/AIDS prevalence: prospective observational study

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U.M., D.N.D., M.B. and K.I.B. devised the protocol of the study, with U.M. overseeing the whole study. T.K., R.G., U.M., J.A., M.M. and D.v.d.M. were responsible for data collection as well as causality, severity and preventability assessment of individual ADRs. K.I.B. and M.B. were also involved in assessment of cases. U.M., D.N.D. and K.I.B. analysed the data. U.M. produced the first draft and all authors contributed to the final draft of the manuscript. U.M. and K.I.B. are guarantors of the study.

**Keywords**
pharmacovigilance, HIV/AIDS, adverse drug reactions, hospitalisation, drug-related morbidity

**Received**
29 May 2007

**Accepted**
8 August 2007

**Published *OnlineEarly***
7 December 2007

## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Studies conducted primarily in developed countries have shown that adverse drug reactions (ADRs) are a significant cause of hospital admission, prolong hospital stay and consequently increase the cost of disease management in patients.
- Cardiovascular medicines, hypoglycaemic agents, nonsteroidal anti-inflammatory drugs and antibiotics are the most frequently implicated medicines in these studies.
- A large proportion of these ADRs have been shown to be preventable through improved drug prescribing, administration and monitoring for adverse effects.

## WHAT THIS PAPER ADDS

- This is the first Sub-Saharan African study in the HIV/AIDS era that describes the contribution of ADRs to patient morbidity, hospitalisation and mortality.
- Cardiovascular medicines and antiretroviral therapy contributed the most to community-acquired ADRs at the time of hospital admission while medicines used for opportunistic infections (such as antifungals, antibiotics and antituberculosis medicines were most frequently implicated in hospital acquired ADRs.
- ADRs in HIV-infected patients were less likely to be preventable.

## AIMS

To describe the frequency, nature and preventability of community-acquired and hospital-acquired adverse drug reactions (ADRs) in a South African hospital serving a community with a high prevalence of human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome.

## METHODS

A 3-month prospective observational study of 665 adults admitted to two medical wards.

## RESULTS

Forty-one (6.3%) patients were admitted as a result of an ADR and 41 (6.3%) developed an ADR in hospital. Many of the ADRs (46.2%) were considered preventable, although less likely to be preventable in HIV-infected patients than in those with negative or unknown HIV status (community-acquired ADRs 2/24 *vs.* 35/42; $P < 0.0001$; hospital-acquired ADRs 3/25 *vs.* 14/26; $P = 0.003$). Patients admitted with ADRs were older than patients not admitted with an ADR (median 53 *vs.* 42 years, $P = 0.003$), but 60% of community-acquired ADRs at hospital admission were in patients <60 years old. Among patients <60 years old, those HIV infected were more likely to be admitted with an ADR [odds ratio (OR) 2.32, 95% confidence interval (CI) 1.17, 4.61; $P = 0.017$]. Among HIV-infected patients, those receiving antiretroviral therapy (ART) were more likely to be admitted with an ADR than those not receiving ART (OR 10.34, 95% CI 4.50, 23.77; $P < 0.0001$). No ART-related ADRs were fatal. Antibiotics and drugs used for opportunistic infections were implicated in two-thirds of hospital-acquired ADRs.

## CONCLUSIONS

ADRs are an important, often preventable cause of hospitalizations and inpatient morbidity in South Africa, particularly among the elderly and HIV-infected. Although ART-related injury contributed to hospital admissions, many HIV-related admissions were among patients not receiving ART, and many ADRs were associated with medicines used for managing opportunistic infections.

## Introduction

Detection of adverse drug reactions (ADRs) in hospitals provides an important measure of the burden of drug-related morbidity on the healthcare system. Studies have shown that the proportion of patients admitted with ADRs ranges from approximately 2.0% to 21.4%, whereas between 1.7% and 25.1% of hospital inpatients are reported to have developed an ADR while in hospital [1–4]. Meta-analyses and reviews of these studies have contributed to the recognition of drug safety as a major public health priority [5–8]. Most of these studies have been conducted in developed countries where disease prevalence, access to medicines, drug use patterns and drug management systems differ markedly from those of developing countries [9]. These differences impact on the frequency and nature of ADRs [6]. Studies to determine the frequency and nature of ADRs in Sub-Saharan Africa during the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) pandemic have not been reported.

Approximately 11.6% of the total South African population is infected with HIV, one the highest burdens in the world [10, 11]. As a result of the HIV pandemic the incidence of tuberculosis (TB) has also risen sharply to an incidence of 600 cases per 100 000 of the total population per year [12]. Antiretroviral therapy (ART) was introduced on a large scale into the public sector in the Western Cape province in April 2004. As both HIV/AIDS and TB are managed with long-term combination treatment regimens, the likelihood of drug–drug and drug–disease interactions is increased. The frequency, nature and population at risk of drug-related harm could thus be different from that seen in developed countries, where the burden of these diseases is low.

This study aimed to determine the frequency of community-acquired and hospital-acquired ADRs, in adult medical wards at a secondary level hospital in Cape Town, South Africa. The secondary objectives were to characterize the nature of the ADRs observed and drugs implicated; to identify predisposing factors for ADRs; and to determine the proportion that were preventable.

## Methods

This prospective observational study was conducted in the Cape Town metropolitan area at New Somerset Hospital, a 300-bed public sector, secondary level teaching hospital. In 2005, antenatal surveys estimated the prevalence of HIV in the Western Cape at approximately 15.03%, with some districts being served by New Somerset Hospital to be as high as 29% [13]. All adult patients (≥16 years old) admitted to the 57 beds in the two main medical wards from 5 September to 29 November 2005 were included in the study. Transfers between study wards were considered part of the same admission. Length of ward stay and hospital stay per patient were determined by calculating the total number of bed days spent by the patient in the study medical wards and in the hospital, respectively.

During the study period a clinical pharmacology team prospectively assessed all admissions to the study wards to determine whether patients were admitted as a result of a suspected ADR or whether an ADR had occurred during admission. The team, comprising a clinical pharmacist, four clinical pharmacology registrars and a hospital pharmacist, assessed each patient record for ADRs a minimum of three times a week for the duration of the study. Two clinical pharmacology consultants assisted with assessing these cases for causality, severity and preventability. Most of the reviewers are currently directly involved with clinical care of patients in the public sector, which facilitated their ability to assess the preventability of these ADRs within the local context. All patient records that had not been assessed completely during the admission were reviewed again following discharge.

A list of trigger events requiring further assessment for drug-related causes (Table 1) was adapted from Rozich to increase sensitivity to possible ADRs [14]. This list was provided to all clinical staff as a pocket reference and displayed on posters in the doctors' and nurses' stations in these wards. Clinicians and nurses from the wards and casualty department were informed about the study and trained in the basic principles of detecting ADRs. They were regularly reminded to obtain a comprehensive drug history from patients at the time of admission and to record this and any suspected ADRs in the patients' chart, as an important component of quality patient care.

The World Health Organization (WHO) definition of an ADR was used [15]. Relapses in the patient's underlying medical condition due to noncompliance or intentional overdose were not included as ADRs. However, unintentional overdoses that gave rise to an ADR were included. Patients were excluded from the analysis when their medical records were unavailable for review, either during the admission or following discharge.

As some patients had more than one ADR during the same hospital admission, the total number of ADRs was greater than the total number of patients experiencing a reaction. In cases where an identical reaction occurred more than once in the same patient during the same hospital stay (e.g. repeated hypoglycaemic episodes), the patient was documented as having experienced a single reaction.

Causality was assessed using the WHO criteria for causality assessment [15]. Adverse events considered as possibly, probably or definitely due to a drug were included as ADRs. Events were categorized into Type A (dose related) or B (idiosyncratic) reactions [16]. The severity of each

**Table 1**

List of trigger and process identified

| Trigger | Process identified |
|---|---|
| **Drug triggers** | |
| **Diphenhydramine, prochloperazine, promethazine (or new antihistamine script)** | Hypersensitivity or drug effect |
| **Parenteral or topical corticosteroid*** | Hypersensitivity reaction |
| **Vitamin K or fresh frozen plasma*** | Over-anticoagulation with warfarin |
| **Metoclopramide or other antiemetic*** | Nausea or emesis related to drug use |
| **Naloxone** | Respiratory depression with narcotic |
| **Antidiarrhoeals** | Drug-induced diarrhoea |
| **Sodium polystyrene** | Hyperkalaemia from renal impairment/drug effect |
| **Insulin with glucose*** | Hyperkalaemia from renal impairment/drug effect |
| **Dextrose 50%*** | Hypoglycaemia – possibly with insulin |
| **Flumazenil** | Oversedation with benzodiazepines |
| **Protamine sulphate*** | Heparin toxicity |
| **Phenytoin stat*** | Drug-induced seizure |
| **Adrenalin*** | Anaphylaxis/bronchospasm |
| **Warfarin*** | Requires vigilance for drug interactions and ADRs |
| **Biperidin*** | Extrapyramidal effect to phenothiazine |
| **Atropine*** | Drug-induced bradycardia |
| **Laboratory triggers** | |
| **Potassium <3.5 mmol $l^{-1}$** | Hypokalaemia related to drug use (e.g. diuretics) |
| **PTT >100 s** | Over-anticoagulation with heparin |
| **INR >5** | Over-anticoagulation with warfarin |
| **WBC < 3000 × $10^6$ $\mu l^{-1}$** | Neutropenia related to drug or disease |
| **ALT >3x normal*** | Hepatotoxicity, possibly drug related |
| **Bilirubin >2x normal*** | Hepatotoxicity, possibly drug related |
| **Serum glucose ≤2.2 mmol $l^{-1}$ *** | Hypoglycaemia related to insulin/oral hypoglycaemic use |
| **Rising serum creatinine to above normal range** | Renal insufficiency related to drug use |
| ***Clostridium difficile*-positive stool** | Exposure to antibiotics |
| **Digoxin, phenytoin, lidocaine, aminoglycosides, vancomycin, theophylline, paracetamol or drug levels reported higher than laboratory therapeutic range** | |
| **Event triggers** | |
| **Oversedation, lethargy, falls*** | Related to overuse of medication |
| **Rash or ulceration** | Drug-related adverse event |
| **Lip swelling/angio-oedema*** | Drug-related adverse event |
| **Seizures/dizziness*** | CNS adverse drug event, drug toxicity |
| **Dystonia, ataxia, torticolis, dyskinesia*** | CNS adverse drug event, drug toxicity |
| **Decreased level of consciousness*** | CNS adverse drug event, drug toxicity |
| **New arrhythmia*** | Drug-related cardiac event |
| **New onset jaundice*** | Drug-related hepatotoxicity |
| **New hypotension (blood pressure: systolic <90 mmHg with or without diastolic <60 mmHg)*** | Drug-related vascular event |
| **New cardiac failure*** | Drug-related cardiotoxicity |
| **Bronchospasm*** | Allergic reaction |
| **Abrupt medication stop** | Adverse event |
| **Transfer to higher level of care** | Adverse event |
| **Event suspected to be drug-related by doctor or nurse** | Suspected ADR |

*Event added or modified from trigger event list published by Rozich [14]. PTT, Partial thromboplastin time; INR, international normalized ratio; WBC, white blood cells; ALT, alanine aminotransferase.

reaction was graded according to the categories defined by Temple and colleagues [17]:

- Increased patient monitoring, no patient harm
- Treatment intervention, temporary patient harm
- Initial or prolonged hospitalization, temporary patient harm
- Permanent harm
- Near patient death
- Death.

Preventability was assessed within the local context of clinical care. The review team reviewed the clinical details of each patient, referred to local treatment guidelines and drug monographs (i.e. the South African Medicines Formulary). If the clinical pharmacology team positively identified one or more preventability criteria as defined by Schumock and Thornton, then the reaction was classified as 'preventable' [18]:

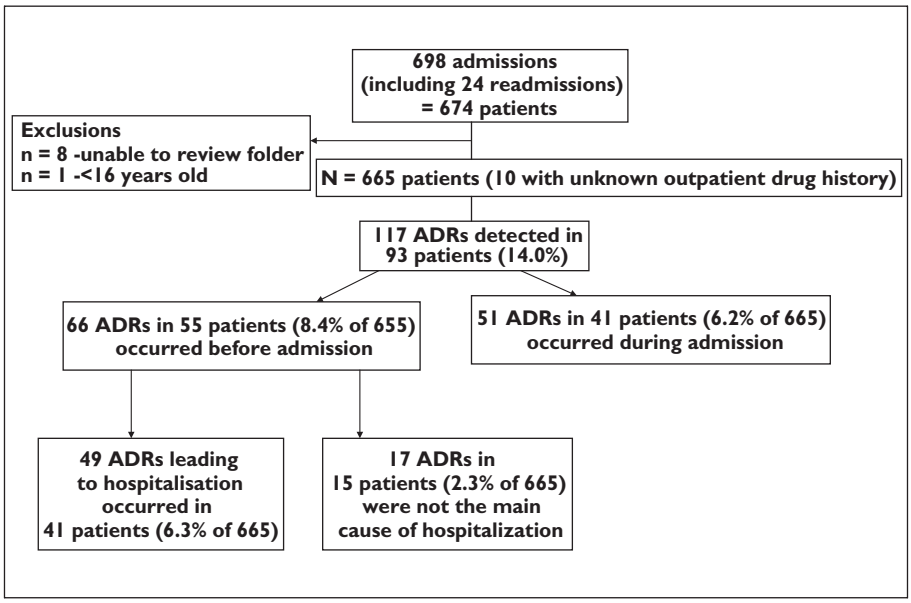
**1** Was the drug involved in the ADR not considered appropriate for the patient's age, weight and disease state?
**2** Was the dose, route or frequency of administration not appropriate for the patient's age, weight and disease state?
**3** Was required therapeutic drug monitoring or other necessary laboratory testing not performed?
**4** Was there a history of allergy or previous reactions to the drug?
**5** Was drug interaction involved in the reaction?
**6** Was toxic serum drug level documented?
**7** Was poor compliance (deviation from the recommended dose) involved in the reaction?

Length of stay was calculated separately for each admission and used to determine the total number of bed days and the median length of stay. The ADR admission rate was determined based on the number of patients admitted at least once with an ADR during the study period.

## *Statistical analysis and ethical issues*

A sample size of 600 was calculated as necessary for detecting an ADR incidence of 6.7% with a 95% confidence interval (CI) of 4.7–8.7%, based on an international systematic review [6]. Data entry and analysis were performed using Microsoft® Excel 2003, and Statistical Program for Social Sciences version 12.0, 2004 (SPSS Inc., Chicago, IL, USA) for Windows. Proportions were compared by $\chi^2$ with Yates' correction or Fisher's exact tests, as appropriate. Nonparametric data were summarized using medians and interquartile ranges (IQR) and compared using the Kruskal–Wallis test.

Approval for the study was obtained from the University of Cape Town Faculty of Health Sciences research




*** Three patients admitted with an ADR developed another ADR while in hospital**

**** One patient admitted with an ADR that caused admission had another ADR that may have contributed to but unlikely to have caused admission.**

**Figure 1**

Distribution of patients experiencing an adverse drug reaction either prior to or during ward admission

ethics committee prior to data collection. Identities of all patients and prescribers were kept confidential.

## Results

### *Details of the cohort*

During the study period there were 698 admissions for 674 patients (Figure 1). In the two study wards, 23 patients were readmitted once ($n = 22$) or twice ($n = 1$) during the study. None of the readmissions was due to an ADR. Eight admissions were excluded as patient records could not be traced, and a single admission was excluded as the patient was <16 years old. Fifteen adverse events were excluded from the analysis as their causal association with drug treatment was considered unlikely. Two cases that were diagnosed with immune reconstitution syndrome were not included as ADRs, as these events were considered to be disease-related unmasking of an underlying opportunistic infection rather than a true ADR. Table 2 describes demographic details of the 665 adult patients included in the analysis and compares the profile of the 572 patients who did not have an ADR with the 93 patients (14%) who were admitted with an ADR ($n = 52$), developed an ADR in hospital ($n = 38$) or experienced both types of ADR ($n = 3$). HIV status was known in 216/665 (32.5%) patients. These patients were younger than those whose HIV status was unknown (median 33 years, IQR 28–41 *vs.* 55 years, IQR 38–68; $P < 0.0001$).

### *Community-acquired ADRs*

A previous medication history was available for 655 patients admitted during the study period. At least one ADR was identified on admission to the ward in 55 (8.4%) patients who presented with 66 ADRs. Of these 55 patients, 41 (6.3%) were judged to have been admitted as a direct result of the ADR and not another condition, whereas in the remaining 14 (2.1%) patients, the ADRs were considered unlikely to have led directly to the admission, although may have contributed to it. In three patients the community-acquired ADRs were judged to have prolonged hospitalization (Table 3).

Patients admitted with ADRs were older than those admitted without an ADR (median 53; IQR 35–73 *vs.* 42; IQR 30–60, $P = 0.003$) (Figure 2). Among patients <60 years old, HIV-infected patients were twice as likely to be admitted with an ADR compared with patients who were HIV– or whose HIV status was not known [21/212 *vs.* 12/281; odds ratio (OR) 2.32, 95% CI 1.17, 4.61; $P = 0.017$]. Among HIV-infected patients, those on ART were 10 times more likely to be admitted with an ADR than those not on ART (14/35 *vs.* 7/181; OR 10.34, 95% CI 4.50, 23.77; $P < 0.0001$).

Cardiovascular medicines (such as ACE inhibitors, diuretics and warfarin) ($n = 22$), antiretroviral (ARV) medicines ($n = 17$), oral hypoglycaemic agents ($n = 7$) and

## Table 2

Demographics of study patients

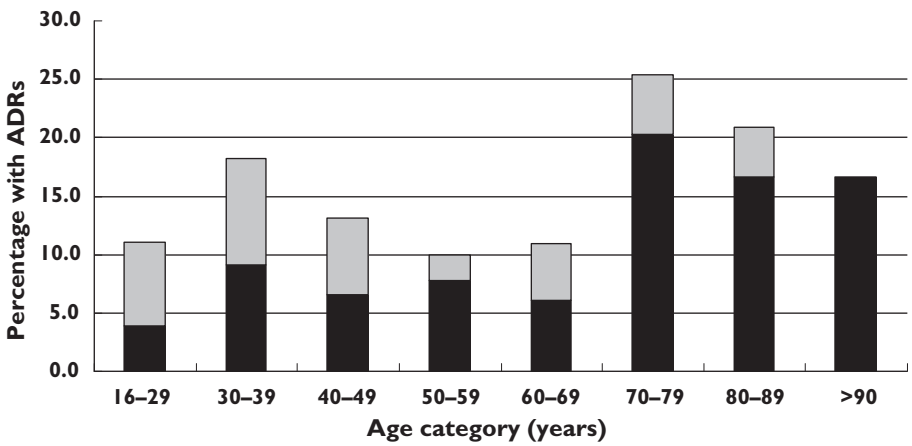
| Characteristic | All patients included | Patients with no ADRs | All patients with ADRs | Patients with ADRs on admission | Patients with ADRs during hospital stay |
|---|---|---|---|---|---|
| **Number of patients** | 665 | 572 | 93 | 55 | 41† |
| **Age in years (median and IQR)** | 42 (30–60) | 42 (30–60) | 42 (33–66) | 53 (35–73) | 38 (28–49) |
| **Female (%)** | 340 (51.1) | 288 (50.3) | 52 (55.9) | 32 (58.2) | 21 (51.2) |
| **Median length of stay in hospital** | 6 (4–10) | 6 (4–9) | 10 (6–15.5)* | 8 (5–12) | 14 (10.5–19) |
| **HIV status (% of total)** | | | | | |
| **Positive** | 216 (32.5) | 177 (30.9) | 39 (41.9)* | 21 (38.2) | 19 (46.3) |
| **• on ART** | 35 (5.3) | 20 (3.5) | 15 (16.1)* | 14 (25.5) | 2 (4.9) |
| **• not on ART** | 181 (27.2) | 157 (27.4) | 24 (25.8) | 7 (12.7) | 17 (41.5) |
| **Negative** | 52 (7.8) | 46 (8.0) | 6 (6.5) | 2 (3.6) | 4 (9.8) |
| **HIV status unknown** | 397 (59.7) | 349 (61.0) | 48 (51.6) | 32 (58.2) | 18 (43.9) |
| **Deaths during hospitalization (regardless of cause) (%)** | 80 (12.0) | 68 (11.9)<br>0 (0) | 12 (12.9) | 7 (12.7) | 8 (19.5) |

*$P < 0.05$ when comparing patients with adverse drug reactions (ADRs) and patients with no ADRs. †Includes three patients who were admitted with an ADR and also developed an ADR during hospital stay. ART, Antiretroviral therapy; IQR, interquartile range.

## Table 3

Severity of adverse drug reactions

| Severity (%) | Community-acquired ADRs, $n = 66$ (%) | Hospital-acquired ADRs, $n = 51$ |
|---|---|---|
| **Increased patient monitoring, no patient harm** | 3 (4.5) | 3 (5.9) |
| **Treatment intervention, temporary patient harm** | 14 (14.1) | 38 (74.5) |
| **Initial/prolonged hospitalization, temporary patient harm** | 44 (66.7) | 6 (11.8) |
| **Permanent harm** | 2 (3) | 1 (2) |
| **Near patient death** | 2 (3) | 2 (3.9) |
| **Death** | 1 (1.5) | 1 (2) |




## Figure 2

Distribution of adverse drug reactions by age category (■ % Patients with ADR on Admission; ■ % Patients with ADR during hospital stay). Note: The three patients who experienced both a community-acquired ADR and a hospital-acquired ADR were included in both analyses. In each of these cases the community-acquired and hospital-acquired ADRs were judged to have occurred independently of each other

## Table 4

Description of ADRs

| ADR | Number of cases | Drugs (number of cases)* |
|---|---|---|
| ***Metabolic*** | 24 | Stavudine-based antiretroviral regimen (9) Amphotericin B (4), Spironolactone (2), Hydrochlorothiazide (1), ACE inhibitor (5), insulin (1), Kayexalate (2) |
| **Symptomatic hyperlactataemia (4)** | | |
| **Lactic acidosis (5)** | | |
| **Hypokalaemia (6)** | | |
| **Hyperkalaemia (5)** | | |
| **Hyponatraemia (2)** | | |
| **Hypernatraemia (1)** | | |
| **Gout precipitated (1)** | | |
| ***Renal*** | 17 | Amphotericin B (8), NSAID (5), Antituberculous drugs (1), Enalapril (2), antibiotic (2), Furosemide (1) |
| **Renal dysfunction** | | |
| ***Hepatobiliary*** | 16 | Antituberculous drugs (10), Efavirenz (1), Stavudine (1), antibiotic (2), Fluconazole (1), Phenytoin (1), normal saline infusion (1) |
| **Hepatitis (13)** | | |
| **Hepatomegaly (1)** | | |
| **Hepatic steatosis (1)** | | |
| **Hepatic congestion (1)** | | |
| ***Neurological and psychiatric*** | 15 | Antituberculous drugs (7), Stavudine-based antiretroviral regimen (3), Midazolam (1), morphine (1), antibiotics (2), Carbamazepine (1), Amitriptylline (1), Benzhexal (1), Trifluperazine (1) |
| **Peripheral neuropathy (8)** | | |
| **Oversedation (1)** | | |
| **Insomnia (1)** | | |
| **Confusion exacerbated (1)** | | |
| **Akathisia (1)** | | |
| **Anticholinergic effect (1)** | | |
| **Cholinergic effect (1)** | | |
| **Neuroleptic malignant syndrome (1)** | | |
| ***Haematological*** | 11 | Warfarin (8), Ceftriaxone (1), Clarithormycin (1), NSAID (1), Zidovudine (1) |
| **Elevated INR—no bleeding (3)** | | |
| **Thrombocytopenia (1)** | | |
| **Anaemia (1)** | | |
| ***Endocrine*** | 11 | Oral hypoglycaemics (8) Insulin (2) Corticosteroids (1) |
| **Hypoglycaemia (10)** | | |
| **Hyperglycaemia (1)** | | |
| ***Skin and mucosa*** | 6 | Antibiotics |
| **Rash (4)** | | |
| **Angio-oedema (1)** | | |
| **Phlebitis (1)** | | |
| ***Cardiovascular*** | 8 | Hydrochlorothiazide (1), Spironolactone (1), Atenolol (3), NSAID (1), Enalapril (2) Thrombolytic (1), Theophylline (1) |
| **Hypotension (2)** | | |
| **Supraventricular tachycardia (2)** | | |
| **Ventricular tachycardia (1)** | | |
| **Heart block (1)** | | |
| **Cardiac failure (1)** | | |
| **Fluid overload (1)** | | |
| ***Gastrointestinal*** | 5 | Stavudine-based antiretroviral regimen (3) Azathioprine (1) Erythromycin (1), Amoxicillin/clavulanic acid (1) |
| **Pancreatitis (3)** | | |
| **Nausea (1)** | | |
| **Diarrhoea (1)** | | |
| ***Immune*** | 1 | Trifluoperazine (1) |
| **Leukopenia** | | |
| ***Respiratory*** | 2 | Morphine (1), Diazepam (1) |
| **Respiratory distress** | | |
| ***Musculoskeletal*** | 1 | Hydrochlorothiazide |
| **Gout precipitated** | | |

*More than one drug may be suspected for a single adverse reaction.

nonsteroidal anti-inflammatory drugs ($n = 7$) were the most frequently implicated drugs in community-acquired ADRs (Table 4). The metabolic ($n = 16$, 24.2%), endocrine ($n = 10$, 15.2%), hepatic ($n = 8$, 12.1%) and neuropsychiatric ($n = 8$, 12.1%) systems were most frequently affected.

Of the 66 community-acquired ADRs, 56 (84.8%) were type A reactions and 35 (53.0%) were considered to be preventable. In two cases there was insufficient information to determine preventability. Community-acquired ADRs identified in patients who were HIV infected were 10

times less likely to be preventable than those identified in patients whose HIV status was negative or unknown (22/24 *vs.* 7/42; OR 0.1, 95% CI 0.03, 0.38; $P < 0.0001$). ADRs in patients >60 years old were twice as likely to be preventable compared with those who were ≤60 years (21/25 *vs.* 16/41; OR 2.15, 95% CI 1.42, 3.27; $P < 0.0001$). Of the 35 preventable reactions, therapeutic drug monitoring or other laboratory testing was not performed in 15 cases (42.9%), the suspected drug was inappropriate for the patient's clinical condition in 12 cases (34.3%), and the dose, route or frequency of administration was inappropriate for the age, weight or disease state based on published literature in five cases (14.3%). In two cases (5.7%), non-adherence to the prescribed dosing regimen was identified and in one case (2.9%) a drug interaction was suspected to have contributed to the event.

There were seven deaths in patients who were admitted with an ADR, and one fatal outcome in a 74-year-old woman who developed a midbrain bleed while receiving warfarin therapy was assessed as probably drug related.

Of the total 5925 hospital days assessed during the 3-month study period, at least 345 days (5.8%) were considered drug related based on the total number of bed days occupied by patients admitted because of an ADR ($n = 41$).

### *Hospital-acquired ADRs*

Of the 665 medical inpatients included in the study, 41 (6.3%) developed at least one ADR while in hospital. Three of these patients had been admitted with a community-acquired ADR. One additional patient was admitted with an ongoing ADR that began in the intensive care unit prior to being transferred to the medical ward and thus was treated as a hospital-acquired ADR. A total of 51 different ADRs were identified in these 41 patients (Figure 1). Patients who developed an ADR in hospital were similar in age (median 38; IQR 28–49 *vs.* 43; IQR 30–60; $P = 0.153$) and gender (OR 1.0, 95% CI 0.6, 1.8; $P = 0.993$) to those who did not develop an ADR in hospital. HIV+ status tended to increase the risk of a hospital-acquired ADR (OR 1.8, 95% CI 0.99, 3.3; $P = 0.058$) when compared with those who were HIV– or whose HIV status was unknown. Patients who developed an ADR during their stay in the ward had a significantly greater length of stay in hospital when compared with patients who did not develop an ADR (median 14 days, IQR 9.5–18.5 *vs.* 6 days, IQR 4–10; $P < 0.0001$).

Of the 51 ADRs detected, 38 (74.5%) were classified as type A reactions and 17 (33.3%) were considered preventable. In one instance there was insufficient information to determine whether the ADR was preventable. Of the 17 preventable reactions, the dose, route or frequency of administration was inappropriate for the age, weight or disease state based on published literature in seven cases (43.8%), the suspected drug was inappropriate for the patient's clinical condition in five cases (31.3%), therapeutic drug monitoring or other laboratory testing was not performed in four cases (25%) and a possible error in insertion of the cannula was identified in one case of drug-induced phlebitis.

**Table 5**

Causality assessment distribution of ADRs

| Causality | No. of ADRs, $n = 117$ (%) | Community-acquired ADRs, $n = 66$ (%) | Hospital-acquired ADRs, $n = 51$ (%) |
|---|---|---|---|
| **Definite** | 21 (17.9) | 12 (18.2) | 9 (17.6) |
| **Probable** | 55 (47.0) | 27 (40.9) | 28 (54.9) |
| **Possible** | 41 (35.0) | 27 (40.9) | 14 (27.5) |

Most (74.5%) of the hospital-acquired ADRs were severe enough to require treatment intervention due to temporary patient harm (Table 4) ($n = 38$) and were usually, probably or possibly related to the suspect drug/s (Table 5). In one patient with multiple myeloma, gentamicin-induced acute renal failure was considered to have contributed to the patient's death. Hospital-acquired ADRs identified in patients who were HIV infected were five times less likely to be preventable when compared with those in patients whose HIV status was either negative or unknown (3/25 *vs.* 14/26; OR 0.223, 95% CI 0.073, 0.683; $P = 0.003$). Hospital-acquired ADRs were classified as preventable as frequently in patients >60 years old as in younger patients (6/11 *vs.* 11/40; OR 1.98, 95% CI 0.95, 4.15; $P = 0.147$).

The physiological systems most frequently affected by hospital-acquired ADRs were the renal ($n = 10$, 19.6%), metabolic ($n = 8$, 15.7%), hepatic ($n = 8$, 15.7%) and dermatological systems ($n = 6$, 11.8%). Amphotericin B ($n = 12$, 23.5%), antibiotics ($n = 11$, 21.6%) and anti-TB drugs ($n = 11$, 21.6%) were the most frequently implicated drug classes.

## Discussion

This study has found that ADRs contribute substantially to patient morbidity and hospitalization in South Africa, further increasing the burden and cost of managing adult patients in an overstretched healthcare system. The ADR rate of 14% occurring in this study population was double that, 6.7%, reported in a systematic review of international studies [6] and the fatality rate of 1.5% amongst community-acquired ADRs was approximately five to 10-fold higher than that reported in the USA and UK [7, 19].

Our study highlights the considerable impact of the HIV/AIDS and TB epidemics on the epidemiology of ADRs in this African population. Patients admitted to hospital were considerably younger than those reported in studies conducted in countries with a low burden of HIV/AIDS [2, 19–21]. There was a bimodal age distribution of patients

with ADRs, with frequencies peaking in both younger, primarily HIV-infected individuals and older patient groups (Figure 2). Both these groups are known to have an increased risk of ADRs [19, 22–25]. In this study, ADRs to ARV agents were more frequently reported than usually implicated in developed countries, where cardiovascular, anticoagulant, nonsteroidal anti-inflammatory and hypoglycaemic agents are most frequently associated with ADRs [5, 19, 20, 26]. Severely ill HIV-infected individuals, who were not receiving ARV treatment, frequently developed hospital-acquired ADRs to drugs used to treat opportunistic infections, particularly amphotericin B, anti-TB drugs and antibiotics. Although there was a significant association between length of hospitalization and the occurrence of an ADR while in hospital, the association may not be causal. Patients who developed an ADR in hospital were younger, usually HIV infected, generally not receiving antiretrovirals, and severely ill as evidenced by the trend towards a higher mortality rate (19.5%). Severely ill patients are likely to take more drugs, have prolonged hospitalizations and may be inherently more vulnerable to ADRs [2].

More than half of the ADRs that were considered to have led directly to hospitalization were preventable, whereas almost a third of the hospital-acquired ADRs were preventable. The majority of ADRs were dose-related, type A reactions. These proportions are similar to the median preventability rate of 35.2% (range 18.7–73.2%) reported in a recent international literature review [27]. This category of ADRs needs to be prioritized by hospitals, health science faculties and clinicians, as increased investment and efforts in training, supervision, monitoring and provision of updated drug information could reduce the burden and cost of managing these illnesses [28]. Interestingly, most of the preventable ADRs leading to hospitalization occurred in the elderly, with most ADRs in young, generally HIV-infected patients not being considered avoidable. The high rate of preventable reactions among elderly patients has been reported by other researchers, particularly where polypharmacy, poor health status including compromised renal and liver function, and the frequent use of drugs with narrow therapeutic indices may play an important role [6, 29–31]. As the association between preventability and age was not seen in hospital-acquired ADRs, the increased risk in the elderly may not be due to the effect of age itself, but rather due to poor prescribing, dosing, adherence and inadequate monitoring, which are more frequent in the outpatient setting [29]. Differences in the types of drugs used in the elderly in the outpatient and inpatient setting could also have contributed to these differences in the preventability of ADRs observed. In contrast, patients with HIV have a predisposition to unavoidable, unpredictable allergic reactions and toxicities such as hepatitis, symptomatic hyperlactataemia and pancreatitis, making the prevention of ADRs in HIV-infected patients more challenging [23, 32–34]. This emphasizes the need for further research on the pharmacokinetic and pharmacogenetic profiles of these drugs in patients with HIV/AIDS. The higher proportion of Type A (dose-dependent) ADRs compared with Type B reactions (idiosyncratic) identified in this study, which is similar to that reported in other countries [2, 7, 21], reinforces the need for improved monitoring of drugs with a narrow therapeutic window.

The intensive prospective collection of ADRs at a sentinel site for a defined period was selected as our study methodology as other studies have shown that spontaneous reporting of ADRs by clinicians, even with routine reminders, has not been effective in detecting drug-induced injuries in hospitals [30]. The use of trigger events by the study team and clinicians in the hospitals simplified case detection and reduced the risk of under-recognition of ADRs, a problem that has been identified by others [35–36]. Future studies in countries with high rates of HIV/AIDS may choose to adapt the trigger tool to include other relevant triggers such as elevated serum lactate levels to detect ARV-induced symptomatic hyperlactataemia and lactic acidosis, elevated liver function tests for drug-induced hepatitis and high-dose pyridoxine or low-dose amitriptyline to detect ARV or anti-TB drug-induced neuropathies.

This study has highlighted the importance of considering the contribution of ADRs (and appropriate prevention measures) when estimating the costs of wide-scale implementation of ARV and anti-TB drug programmes. In this study, all ART-related ADRs were nonfatal and resolved with proper management. The risk of ART-related injury must be seen in relation to the cost of not treating patients with ARTs given the high number of HIV-related admissions among patients not on ART as well as the high number of ADRs to medicines used in the management of opportunistic infections. Studies have consistently shown the dramatic decrease in AIDS-related admissions with the introduction of ART in HIV-infected populations [37–39]. Therefore, the findings of this study need to be seen within a broader perspective that takes into account the benefits of using these drugs in managing life-threatening diseases.

## Limitations of the study

Given the limited availability of hospital beds in South Africa, not all patients requiring admission can be hospitalised. Our findings may therefore be an underestimate of the number of community-acquired ADRs. In addition, inaccurate and incomplete medical records, given the high patient loads, frequent staff turnover and limited access to laboratory facilities that are common to many African hospitals may also have contributed to under-recognition of ADRs in this study [35, 36]. Even higher ADR rates have been reported by others [20], although differences in study methodology and setting frequently preclude direct com-

parisons. The results of this study should therefore be extrapolated to other settings with caution, as study findings depend on the patient profiles, healthcare infrastructure, detection methods and definitions of ADRs adopted.

Studies have consistently shown that an important predictor of ADR risk is the number of drugs taken by an individual patient [6, 29, 40]. This may account for the increased risk of ADRs noted in elderly patients and in patients infected with HIV/AIDS and/or TB. However, this measure was not included in our analysis as widely used traditional, complementary and over-the-counter medicines, as well as single dose drugs and drugs used in inpatients on an "as needed" basis, are seldom recorded accurately in drug histories, potentially compromising the validity of these data.

The assessment of causality, severity and preventability is subjective and prone to inter-rater variability. For this reason a consensus approach involving at least four clinicians was employed. The review team was provided with clear peer-reviewed standardised criteria for categorising ADRs. We chose not to use an algorithmic approach to assess the causality of ADRs as the WHO causality assessment criteria incorporate all the elements of most algorithms. Lee and colleagues found a poorer level of agreement of the various algorithmic methods when compared to expert clinical judgment [41]. Minor differences between review team members usually occurred as a result of inadequate information and were resolved through further investigations either by reviewing current clinical practices, the biomedical literature, or by obtaining additional information from the patients' medical records. When considering the preventability of reactions, situations could have arisen where the clinician may have consciously decided to treat a patient with higher doses or more frequently than recommended as a result of the severity of the patient's clinical condition at the time of prescribing without including a justification for this in the medical records.

Although every effort was made to minimize the likelihood of a Hawthorne effect, this cannot be eliminated in a prospective observational study. Clinical staff were not directly involved in the data collection process. Only two investigators rotated through the study wards on any day to review patient records. This was usually conducted after routine medical rounds were completed. Feedback on the results of the study was only provided to hospital staff after the study was completed. It was not possible to assess whether there were any changes in patient management over the study period as a result of the study.

## Conclusion

This study has shown that ADRs are an important cause of admissions and contribute to inpatient morbidity in the public healthcare system in South Africa, with a frequency similar to or greater than that found in studies in developed countries. The majority of reactions were dose related, with a high proportion of reactions being preventable, thus highlighting the importance of improving drug selection, use and monitoring, particularly in vulnerable patient groups. HIV/AIDS appears to be an important determinant of the profile of patients, drugs implicated and nature of ADRs seen in hospitalized patients in a country with a high burden of this disease. Further studies in different settings and at different levels of healthcare in Sub-Saharan Africa are warranted, particularly as the access to life-saving therapies including ARV medicines improves. The use of a standardized, simple methodology would greatly contribute towards a better, shared understanding of the nature and extent of this silent public health problem and the measures that can be taken to minimize the occurrence of preventable reactions.

*Competing interests*

*U.M. is pursuing a Doctor of Public Health degree with a focus on pharmacovigilance. U.M. is a member of the national drug regulatory authority, the Medicines Control Council (MCC) and its pharmacovigilance subcommittee. U.M. frequently serves as a technical advisor for the World Health Organization in matters relating to medicines safety. M.B. is a member of the National Essential Drug List (EDL) Committee and chairperson of the tertiary and quaternary level EDL subcommittee; the Western Cape pharmacy and therapeutics committee; the MCC pharmacovigilance committee and clinical committee; and a member of the UCT Health Sciences Research Ethics committee. M.B. recused himself at the research ethics committee during discussions on the approval of this study. R.G. and T.K. are both employed by the Western Cape provincial department of health. K.I.B. is a member of the Malaria Advisory Group that advises the national department of health on malaria policy.*

*The authors gratefully acknowledge the clinical, nursing and administrative staff at the New Somerset Hospital for their assistance and support in this study. In particular, the authors thank Professor Roal van Zyl-Smit, Dr Barbara Scholtz and Dr Rehana Bobat for their support and for encouraging clinicians and nurses in supporting the study. Dr James Arens, Dr Maria Machai and Mr Dawid van der Merwe are gratefully acknowledged for their valuable contribution as members of the clinical pharmacology team. Sincere thanks to Professor Gary Maartens and Professor van Zyl-Smit for their critical review of the manuscript.*

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